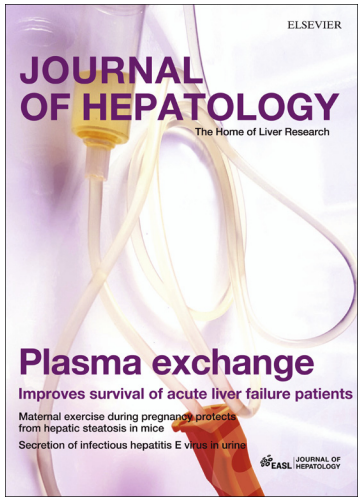


# Minimal hepatic encephalopathy in children, uncommon or unrecognised? - Time to act

Eirini Kyrana, Anil Dhawan

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Authors: Eirini Kyrana[1] and Anil Dhawan[1]

Institution: [1]Paediatric Liver, GI and Nutrition Centre and MOWATLabs King's College Hospital, London

Corresponding author: Professor Anil Dhawan, Paediatric Liver, GI and Nutrition Centre and MOWATLabs at King's College Hospital, Denmark Hill, London, SE5 9RS.

Tel: 0044-2032994408, Fax: 0044-2032993657

E-mail: anil.dhawan@nhs.net

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Authors: Eirini Kyrana[1] and Anil Dhawan[1]

Institution: Paediatric Liver, GI and Nutrition Centre and MOWATLabs, King's College Hospital, London.

Hepatic encephalopathy has been defined as a spectrum of neuropsychiatric abnormalities seen in patients with liver dysfunction after exclusion of an intrinsic brain disease [1]. Minimal hepatic encephalopathy (MHE) has been used to describe a subset of patients with the mildest form of encephalopathy, not detected on clinical examination, but detected on psychometric testing [1, 2]. The term applies to both patients with cirrhosis and patients with portosystemic shunts without intrinsic liver disease like isolated portal vein thrombosis [1]. The assessment of children with chronic liver disease (CLD) for encephalopathy is very challenging, particularly when assessing a frightened, unwell, younger child making it even more difficult to diagnose MHE.

There are a few studies to suggest that children with CLD are at risk of developing a cognitive impairment, which is worse when the disease manifests in the first year of life [3, 4]. These children have been shown to perform worse on measures of verbal, non-verbal and overall intelligence. In addition, liver transplantation does not correct these deficiencies and children post liver transplantation have been shown to have lower overall language skills, a decrease in non-verbal intelligence and lower academic achievements [5, 6]. The precise mechanism for these deficiencies is not known. Nutritional deficiencies are a possible factor, but the presence of MHE and the effect of toxic metabolites on the developing brain could be another. The ability to identify and treat factors that may be affecting the cognitive development of these young patients could have an exponential benefit for these children's long term academic and overall life achievements. We therefore welcome in this edition of Journal of Hepatology the paper by Srivastava et al [7] which endeavours to tackle this very interesting issue of MHE in children with CLD, providing us with some insight into the mechanism of its development as well as indices on imaging that can help diagnose it.

The prevalence of MHE as reported in this study seems to be similar in children and adults at about 50% [8-10]. The ammonia hypothesis suggests that raised ammonia levels lead to an increase of glutamine in brain astrocytes causing them to swell with subsequent neuro-dysfunction with additional contributory factors being endogenous benzodiazepines and the presence of inflammation [11, 12]. MHE in adults with cirrhosis has been associated with a reduced 5 year survival rate [13] and has been associated with reduced quality of life [14].There is no similar data available in children but some neurological abnormalities described with MHE may persist even after liver transplantation [15] making it crucial to detect MHE and offer intervention.

Various modalities have been used to diagnose MHE including EEG, critical flicker frequency, continuous reaction time, inhibitory control test, computerised test

batteries, arterial spin labelling MRI with the psychometric hepatic encephalopathy score (PHES) considered to be the gold standard [16, 17].

Srivastava et al [7] studied prospectively 67 children with CLD and compare them to 37 healthy children. The study evaluates a plethora of parameters that could potentially be associated with MHE, including blood ammonia, IL6 and TNFα levels as well as calculating PELD and MELD scores and classifying their patients according to Child class. The children undergo NPT, magnetic resonance spectroscopy (HMRS) to study brain metabolite changes (specifically glutamine, choline and myoinositol) and also have diffusion tensor imaging (DTI) derived metrics. On the basis of NPT testing the authors find a prevalence of 50.7% for MHE, which is comparable to the one reported by Razek et al [8].

The children with CLD in comparison to the healthy children had relatively higher blood ammonia, but absolute levels were still in the normal range casting some doubts towards the ammonia hypothesis. On HMRS they had higher glutamine and lower choline and myoinositol in their brain. In addition they had a higher T1 signal intensity in the globus pallidus as well as a higher mean diffusivity in all brain regions on DTI, indicating cerebral oedema. Moving on to the more interesting comparisons between the subgroup of patients with MHE and those without MHE we see that between the two groups there was no difference in age, gender or aetiology of the liver disease. The differences in Child class, PELD and MELD score did not achieve statistical significance. This observation may suggest that MHE is more of a phenomenon related to the presence of portal hypertension rather than the degree of hepatic dysfunction.

The patients with MHE had significantly higher glutamine on HMRS. As previously mentioned these patients overall had a higher mean diffusivity on all brain regions on DTI in comparison to the controls, but the patients with MHE had an even higher mean diffusivity in six brain regions including frontal white matter. NPT, which was used to diagnose the MHE, had a significant positive correlation with brain choline and brain myoinositol. NPT had a significant negative correlation with blood ammonia, IL6 and TNFα, brain glutamine and with the mean diffusivity assessed by DTI. This led to the authors analysing and concluding that in fact frontal white matter mean diffusivity was the best discriminator of MHE with a sensitivity of 73.5% and a specificity of 100%.

The study by Srivastava et al [7] provides some insight and a possible explanation for these children's poor school performance, by linking NPT testing with neuroimaging. It would have been interesting if the authors could have also correlated the presence of MHE with school performance. A large proportion of the patients studied had autoimmune liver disease, whereas a more representative cohort of patients with chronic liver disease would include more patients with cholestatic liver disease, who are affected at a younger age. Nevertheless this study brings objective neuroimaging into the evaluation of children with chronic liver disease paving the way for further studies of this kind to evaluate younger children with chronic liver disease for the presence of MHE. Although it is difficult to ascribe neurocognitive complications in children with early onset cholestatic disorders to

MHE solely, the relationship intuitively appears plausible hence an early intervention including liver transplantation could improve long term scholastic and neurocognitive outcomes.

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